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Neuronal correlates of encoding and retrieval in episodic memory during a paired-word association learning task: a functional magnetic resonance imaging study

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Abstract The investigation of memory function using functional magnetic resonance imaging (fMRI) is an expanding field of research. The aim of this study was to demonstrate brain-activity patterns related to a word-pair association task employing a whole-brain EPI sequence. Six right-handed, healthy male volunteers (mean age: 27.5 years) took part in the study. fMRI was performed at a field strength of 1.5 Tesla with 26–32 slices parallel to the AC-PC line, depending on individual brain size. Distributed brain regions were activated in episodic encoding and retrieval with similarities, but also (distinct) differences in activation patterns. Bilateral prefrontal cortical areas were involved when comparing encoding as well as retrieval to the reference condition (nonsense words). Furthermore, activation was observed in cerebellar areas during encoding, and activation in bilateral parietal areas (precuneus and inferior parietal cortex) was differentially more pronounced during retrieval. The activation of left dorsomedial thalamus during retrieval of high imagery-content word-pair associates may point to the role of this structure in episodic retrieval. The direct cognitive subtraction of encoding minus retrieval yielded a differentially larger left prefrontal activation. There was a differentially higher right prefrontal activation during retrieval than during encoding, underlining the proposed right/left asymmetry for episodic memory processes.

Key words Episodic memory · Paired word association · fMRI

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Introduction

Different types of long-term memory systems have been described in the literature. On the one hand, there is explicit memory, which is divided in declarative episodic memory (e.g., paired associate learning and retrieval) or semantic memory (i.e., general knowledge of the world). On the other hand, there is implicit memory, which describes nondeclarative memory (i.e., skills or behavioral procedures) (Tulving 1983, 1985; Fletcher et al. 1995a). Conventionally, episodic memory processes have been separated into two different stages, either involving the processing and incorporation of novel information (encoding) or recollection of previous stored events (retrieval) (Tulving 1983, 1985; Tulving et al. 1994). During retrieval in episodic memory, the unique context associated with a learned episode is accessed as part of the retrieval event. This differs from semantic retrieval, where access to contextual information is not required (Tulving 1983, 1985; Buckner et al. 1995, 1996).

Most theories concerning the organization of the memory system were developed based on animal studies (e.g., Kievit and Kuypers 1977; Asanuma et al. 1985; Yetarian and Pandya 1985; Cavada and Goldman-Rakic 1989a, 1989b) or lesion studies and case reports (e.g., Scoville and Milner 1957; Penfield and Milner 1958; Warrington and Weiskrantz 1982; Zola-Morgan et al. 1986; Schacter 1987; Weiskrantz 1987; Rudge and Warrington 1991). The investigation of cognitive mechanisms using functional neuroimaging has advanced rapidly in the few past years (for reviews, see Tulving et al.

1994; Gabrieli 1998; Nyberg et al. 1998; Schacter and Wagner 1999), where most studies concerning memory functions have been carried out using positron emission tomography (PET).

After the first successful demonstration of brain activity with magnetic resonance imaging (MRI) was presented by Belliveau and co-workers (1991), the use of fMRI in the study of cortical functions evolved rapidly (Bandettini et al. 1992; Le Bihan et al. 1993; McCarthy et al. 1994; Demb et al. 1995; D'Esposito et al. 1995; Buckner et al. 1996; Spitzer et al. 1996; Stern et al. 1996; Busatto et al. 1997; Cohen et al. 1997; Gabrieli et al. 1997; Kelley et al. 1998; Wagner et al. 1998). The rapid acceptance of fMRI as a method for investigation of brain function is based on the lack of ionizing radiation, its complete non-invasiveness, and, as compared with PET, the higher spatial resolution (Le Bihan 1996). The non-invasive nature of the technique confers the significant advantage that longitudinal studies, and thereby easier optimization of paradigms, become possible.

In particular, the investigation of memory function using fMRI is an expanding field of research (Le Bihan et al. 1993; McCarthy et al. 1994; Demb et al. 1995; D'Esposito et al. 1995; Buckner et al. 1996; Spitzer et al. 1996; Stern et al. 1996; Busatto et al. 1997; Cohen et al. 1997; Gabrieli et al. 1997; Kelley et al. 1998; Wagner et al. 1998). Recent studies have evaluated working memory tasks (Demb et al. 1995; D'Esposito et al. 1995; Buckner et al. 1996; Gabrieli et al. 1997) or episodic memory (Busatto et al. 1997; Kelley et al. 1998; Wagner et al. 1998).

In most of the recent fMRI studies of memory, EPI sequences covering only parts of the brain (e.g., prefrontal cortex, hippocampal area) have been used, omitting important brain areas likely to be involved in the distributed processing of semantic and episodic memory. To our knowledge, our study is one of the first to apply whole-brain-coverage fMRI in the field of memory research, showing the disperse cortical areas being involved in episodic memory encoding and retrieval. Our intention was to disentangle the different brain regions involved in paired-word association learning and retrieval.

Material and methods

Subjects

A total of six right-handed (according to the Edinburgh handedness scale: Oldfield 1971) male volunteers (mean age: 27.5±1.4 years) with no history of neurological or psychiatric illness took part in the study, which was approved by the local ethical committee and federal authorities. All subjects gave informed, written consent for participation in this study.

fMRI

Functional MR imaging was performed on a 1.5 Tesla MRI system (Siemens Magnetom Vision, Erlangen, Germany), equipped with EPI capabilities and a transmit/receive head coil. The subjects were positioned in the scanner with the head immobilized using foam supported cushions. Sequences with the following parameters were employed: gradient echo EPI; repetition time (TR)=5 s; echo time (TE)=66 ms; field-of-view (FOV)=200 mm; flip angle (θ)=90°; matrix size=64×64, giving an in plane pixel size of 3.13×3.13 mm^2. Using a midsagittal scout image, 26–32 axial slices (4 mm thickness and 0.4 mm interslice gap) were oriented along the anteriorposterior commissure (AC-PC) line. In addition, high-resolution anatomical images of the brain were obtained by using the 3D MP-RAGE sequence (rapid acquisition gradient echo) with the following sequence parameters: TR=11.4 ms; TE=4.4 ms; θ=15°; FOV=200 mm; matrix size=200×256; 128 sagittal slices with a thickness of 1.41 mm or 1.33 mm.

Table 1 Memory performance of the subjects (in % correct) immediately after the scanning (performance 1) and 1 week later (performance 2). The presentation rate depended on the prescanning testing. Subjects were presented with a different word-pair set prior the actual experiment until they retrieved about 70% of the to be encoded material

Subject	Memory performance		
	Performance 1	Performance 2	Presentation rate
1	100	92	2
2	100	100	3
3	92	50	2
4	100	100	2
5	66	17	5
6	100	92	4
Mean	93	75	

During each experimental condition, a series of 21 EPI whole-brain data sets were acquired. Each series consisted of a baseline period followed by an activation period and terminated with a baseline period. Each subject underwent four sessions. During the first session, the subjects were presented with the single or paired nonsense words, respectively, during activation. The second session served for the first presentation of the word-pairs that had to be encoded during the activation period. Between the second and the third session, the subjects were presented with the word-pairs as often as necessary, according to the individual performance tested prior to scanning (Table 1). During the third session, the retrieval condition was presented. The fourth session again was the presentation of single or paired nonsense words, respectively. During the baseline periods, subjects heard only the ambient machine noise, but did not perform the memory task, while during the activation period, during which the visual-verbal memory task or the reference task was switched on, the subjects were required to perform the memory task or read the nonsense words silently. Each series began with nine baseline data sets, three of which were discarded to allow the MR signal to reach equilibrium and an initial baseline to be established. This was followed by the acquisition of six data sets, during which activation stimulus was present, and a final baseline of six data sets. The total duration of each image series was 105 s.

Paired word association learning

A visual-verbal declarative memory task was evaluated. Subjects were presented visually with word-pairs of high imagery content, which were not semantically related. These "hard" word associations (Wechsler 1945) were used to increase the mnestic demands. Study words were two-syllable German words that were between four and seven letters in length and of moderate frequency (Meier 1964). Baschek and co-workers (1977) evaluated 800 German words of moderate frequency with respect to their imagery content in a group of 80 students based on a work by Paivio (1966). An imagery score was established ranging from 1–7, 1 being of low

(i.e., abstract) and 7 of high imagery content. For our study, we used high-imagery-content words in the range between 5 and 7. Word pairs (with the second word presented under the first to avoid lateralization effects) were presented on a translucent screen placed at a distance of about 50 cm from the eyes. Subjects viewed the words with the aid of an overhead mirror. The letters were white on a black background and centered. The presentation of single nonsense words (reference II) or nonsense word-pairs (reference I) served as reference conditions. The subjects were instructed to read the nonsense words silently without learning them. The nonsense words were two syllable pseudowords with 4–7 letters and obeyed German spelling rules.

Prior to scanning, all subjects underwent memory-performance testing. Subjects were presented with 12 word pairs while lying in the magnet. Immediately afterwards, they were asked to retrieve the corresponding word-pair associate after randomized presentation of the first words of each word pair. Individual performance was evaluated by repeating the storage and retrieval task for the number of times the volunteer needed to successfully retrieve about 70% of the randomly presented word pairs (Table 1).

During scanning, a different set of 12 word pairs was presented as often as the previously determined individual performance required. We only used the first encoding of the word pairs for the analysis. In the subsequent retrieval condition, the first words of each word pair were again randomly presented. Subjects were asked to retrieve the associated word by using inner speech to prevent movement artifacts. The subjects were only presented once with the retrieval condition. Immediately after scanning, recall accuracy was tested.

Data analysis

Image analysis was performed on a SPARC Ultra 1 workstation (Sun Microsystems) using MatLab (Version 4.2c) and the SPM96 software (SPM software, The wellcome Department of Cognitive Neurology) (Friston et al. 1994a, 1994b, 1995a, 1995b, 1995c; Poline et al. 1995; Worsley and Friston 1995).

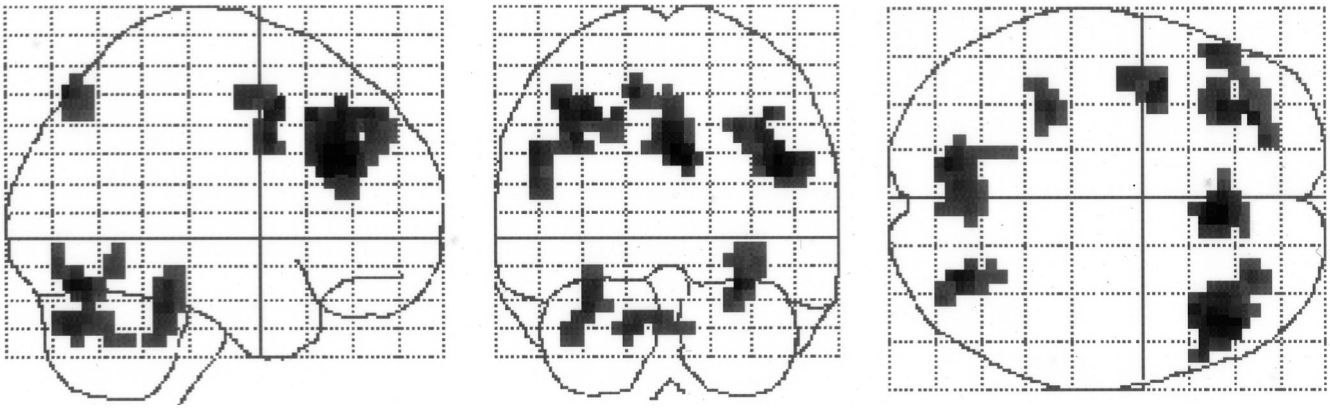
First, the 18 volume images of each condition were automatically realigned to the first image to correct for head movement between scans (Friston 1995a). The data sets of the encoding and retrieval conditions were then co-registered with the 3D anatomical image and transformed into the standard stereotactic space corresponding to the atlas of Talairach and Tournoux (1988). Within this normalization, the voxels of the 3D image were slightly smoothed to achieve an isotropic voxel size of 4×4×4 mm (Poline et al. 1995). Voxels that had values greater than 0.8 of the volume mean in all the images were selected to restrict that analysis to intracranial regions. Low frequency artifacts arising from aliased cardiorespiratory and other cyclical components were removed with high-pass filtering (0.5 cycles/min) of the time series. In order to present the overall pattern of activation across subjects, the stereotaxically transformed functional data sets from each subject were slightly smoothed with a Gaussian filter with a root-mean-square radius of 8 mm to compensate for inter-subject differences and to suppress high-frequency noise in the images. With these data, group activation maps were calculated by pooling the data for each condition across all six subjects. The alternating periods of baseline and activation were modeled using a simple smoothed, delayed box-car reference vector to take account of the delayed cerebral blood flow changes after stimulus presentation. Significantly activated voxels were searched for by using the "general linear model" approach for time-series data (Friston et al. 1994a, 1994b, 1995a, 1995b, 1995c; Poline et al. 1995; Worsley and Friston 1995). For this, we defined a design matrix comprising contrasts testing for significant activations during episodic encoding versus reference I and retrieval versus reference II. Voxels were identified as significantly activated if they passed the height threshold of z=2.33 (P<0.01) and at least belonged to a cluster of 20 activated voxels (k=20). For the cognitive subtraction "encoding minus reference I" versus "retrieval minus reference II" and vice versa, an additional design matrix was defined with a more lenient threshold (z=1.65; P<0.05; k=20). The activated voxels surviving this procedure were superimposed on SPM glass brain projections (see Figs. 1, 2, 3, 4). With the aid of published Talairach-coordinates (Talairach and Tournoux 1988), clusters of activated voxel were assigned according to their center-of-mass activation.

Results

Memory performance

The prestudy training period was carried out to assess the individual presentation rate at which recognition performance was above 70%. Post-measurement questioning of the subjects after the fMRI measurement (2–5 presentations, depending on individual performance) resulted in a high overall recognition performance of 93%±13.6% (Table 1). Most of the subjects used imagery when recalling the high imagery content items in the episodic memory task. In addition, we could show that the subjects had stored the learned word-pairs into long-term memory by testing them 1 week later with the same retrieval task (75.2%±34.1%). The performance was about 80% of the words initially learned (t-test: P=0.051; Table 1).

Fig. 1 Encoding of word-pairs minus reference I. Spatial distributions of significantly activated voxels are shown as integrated projections along sagittal, coronal (image right is subjects right), and transverse (image top is subjects left) views of the brain (from left to right)



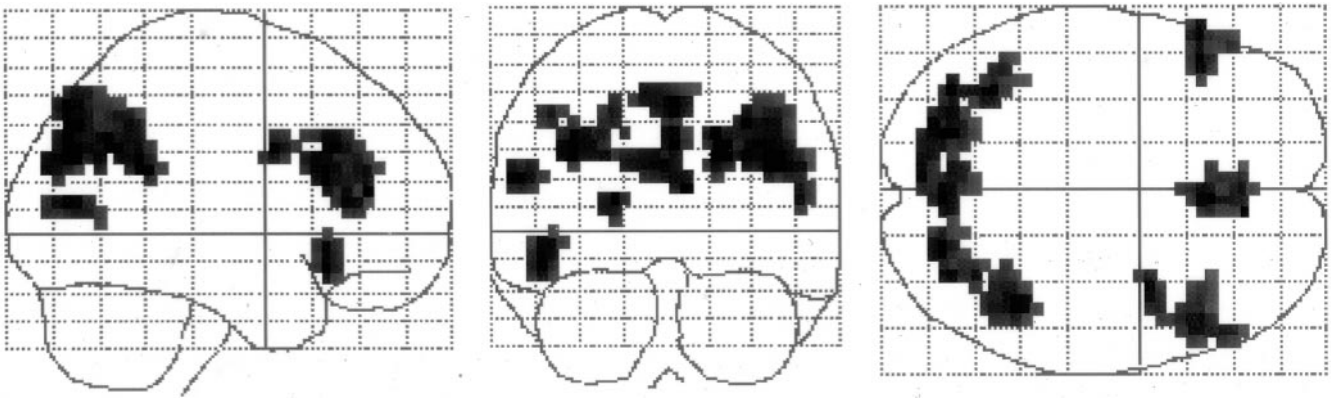


Fig. 2 Retrieval of word-pair associates minus reference II. Spatial distributions of significantly activated voxels are shown as integrated projections along sagittal, coronal (image right is subjects right), and transverse (image top is subjects left) views of the brain (from left to right)

Table 2 The stereotactic coordinates (*x*, *y*, *z*) of maximal activations (increase in BOLD signal) for encoding word-pairs minus reference I (nonsense word-pairs). Coordinates are according to the atlas of Talairach and Tournoux (1988), areas are named after Brodmann (*BA*). The voxels show levels of significance above a threshold *z*=2.33, *P*=0.01, and a cluster size of *k*=20

	z	x	y	z	BA
Precuneus, left	3.56	–12	–76	52	7
Precuneus, right	2.83	4	–68	48	7
Cerebellum, left	3.27	–32	–36	–24	
Cerebellum, right	3.82	28	–72	–16	
Anterior cingulate	4.47	8	32	28	32
Prefrontal, left	3.76	–32	32	44	8
	3.73	–40	8	48	6
	3.40	–52	28	32	9/46
Prefrontal, right	4.38	44	36	28	9/46
	3.49	40	20	44	8
Parahippocampal, left	3.02	–28	–36	–16	

Table 3 The stereotactic coordinates (*x*, *y*, *z*) of maximal activations (increase in BOLD signal) for retrieval minus reference II (single nonsense words). Coordinates are according to the atlas of Talairach and Tournoux (1988), areas are named after Brodmann (*BA*). The voxels show levels of significance above a threshold *z*=2.33, *P*=0.01, and a cluster size of *k*=20

	z	x	y	z	BA
Secondary visual areas	3.83	20	–76	32	19
Precuneus, left	3.04	–8	–72	52	7
Precuneus, right	3.48	4	–76	48	7
Anterior cingulate	3.74	8	40	16	32
Prefrontal, left	3.46	–56	24	20	45
	2.95	–52	36	24	9/46
	3.46	–48	24	–12	47
Prefrontal, right	3.36	36	4	32	44/46
Parietal inferior, left	3.45	–36	–72	28	39/40
Parietal inferior, right	3.56	44	–48	28	40

Pooled analyses

Encoding of word-pairs compared with reference I: increases in the BOLD signal

During encoding of word pairs, significant increases of the BOLD signal were observed in the left (BA 7, *z*=3.56) and right (BA 7, *z*=2.83) precuneus, the anterior cingulate (BA 32, *z*=4.47), in three distinct left frontal cortical areas including parts of the supplementary and pre-supplementary motor cortex (BA 6, *z*=3.73; BA 8, *z*=3.76; BA 9/46, *z*=3.40), two distinct right frontal cortical areas (BA 8, *z*=3.49; BA 9/46, *z*=4.38), and in the left dorsal parahippocampal area (*z*=3.02) (Table 2, Fig. 1). A significant increase of the BOLD signal was also observed in bilateral cerebellar areas with a larger cluster size on the left side (left, *z*=3.27, *k*=41; right, *z*=3.82, *k*=20).

Retrieval of word-pair associates compared with reference II: increases in the BOLD signal

Significant increases in the BOLD signal comparing the retrieval of word-pair associates with reference II were seen in the left (BA 7, *z*=3.04) and right (BA 7, *z*=3.48) precuneus, the visual integration area (BA 19, *z*=3.83), in the right frontal cortex (BA 44/46, *z*=3.36), in three distinct left frontal cortical areas (BA 45, *z*=3.46; BA 47, *z*=3.46; BA 9/46, *z*=2.95), and the anterior cingulate

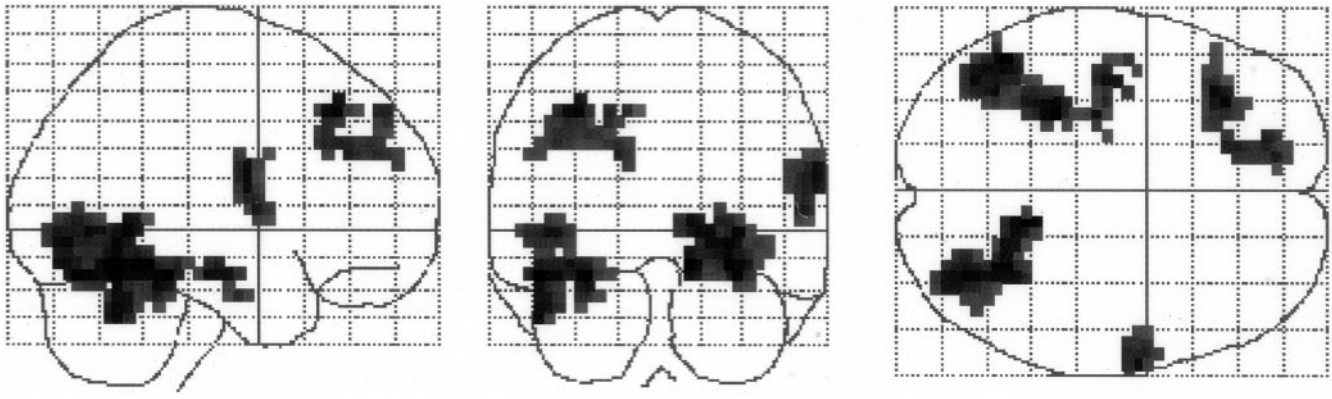


Fig. 3 Encoding minus reference I versus retrieval minus reference II of word-pair associates. Spatial distributions of significantly activated voxels are shown as integrated projections along sagittal, coronal (image right is subjects right), and transverse (image top is subjects left) views of the brain (from left to right)

Table 4 The stereotactic coordinates (*x*, *y*, *z*) of maximal activations (increase in BOLD signal) for encoding minus reference I versus retrieval minus reference II. Coordinates are according to the atlas of Talairach and Tournoux (1988), areas are named after Brodmann (*BA*). The voxels show levels of significance above a threshold z=1.65, P=0.05, and a cluster size of k=20

	z	x	y	z	BA
Cerebellum, left	2.85	–48	–6	–32	
Cerebellum, right	3.24	12	–44	–12	
Prefrontal, left	3.02	–32	32	44	8
	2.53	–16	36	28	9
Prefrontal, right	2.76	64	–4	20	6
Temporal, left	3.10	–28	–36	–16	20
	3.09	–48	–56	–16	37
Parahippocampal, left	2.77	–28	–20	–16	

(BA 32, z=3.74) (Table 3, Fig. 2). An augmentation of the BOLD response was also seen in the left (BA 39/40, z=3.45) and right (BA 40, z=3.56) inferior parietal cortex. At a more lenient threshold (z=2.2; cluster size: k=13), there was a left side dorsolateral thalamic activation (z=3.13).

Encoding versus retrieval of word-pair associates: increases in the BOLD signal

For the direct cognitive subtraction encoding versus retrieval and vice versa, a more lenient threshold (z=1.65; P=0.05) was chosen to be able to comprise all important significantly activated regions (Table 4, Fig. 3). Bilateral cerebellar activation (left: z=2.85; right: z=3.24) were found for the cognitive subtraction analysis "(encoding minus reference I) minus (retrieval minus reference II)". Further significant increases included bilateral prefrontal activations augmented on the left (left: BA 8, z=3.02, BA 9, z=2.53; right: BA 6, z=2.76) and a large activation cluster in the left temporal lobe comprising the inferior temporal lobe (BA 20, z=3.10), the fusiform gyrus (BA 37, z=3.09), and the left parahippocampal area (z=2.77).

Retrieval versus encoding of word-pair associates: increases in the BOLD signal

The significantly differentially more activated regions of "(retrieval minus reference II) minus (encoding minus reference I)" were the left (BA 7/19, z=2.80) and right (BA 7/19, z=2.51) precuneus, left (BA 39/40, z=3.63) and right (BA 40, z=2.51) medial and inferior parietal cortex, and bilateral frontal regions with augmentation on the right (left: BA 6, z=2.79; right: BA 45, z=2.43) (Table 5, Fig. 4). With a smaller cluster size (k=10), there was significant activation in the left dorsal thalamus (z=2.03).

Single-subject analysis

Comparing pooled with single-subject analyses, there were similarities in activation patterns, but also intersubject variability. The prefrontal left or right cortex reached significant activation clusters in three of the six subjects during encoding and in all subjects during retrieval. Anterior cingulate activation was present in four of six subjects during both encoding and retrieval. The precuneus showed significant activation in four of six subjects during retrieval. Bilateral activations in the inferior parietal cortex were seen in four of six subjects.

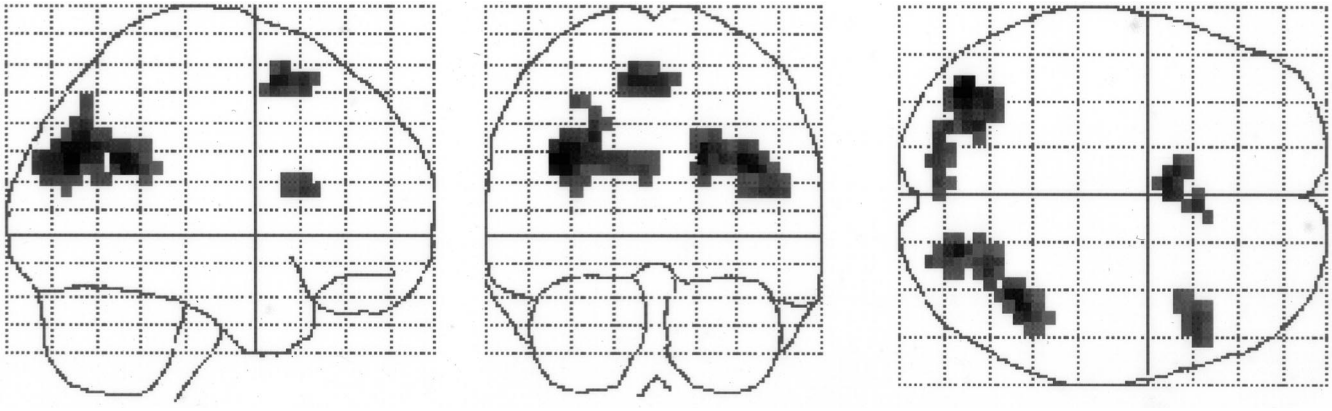


Fig. 4 Retrieval minus reference II versus encoding minus reference I of (image top is subjects left) word-pair associates. Spatial distributions of significantly voxels are shown as integrated projections along sagittal, coronal (image right is subjects right), and transverse (image to is subjects left) views of the brain (from left to right)

Table 5 The stereotactic coordinates (*x*, *y*, *z*) of maximal activations (increase in BOLD signal) for retrieval minus reference II versus encoding minus reference I. Coordinates are according to the atlas of Talairach and Tournoux (1988), areas are named after Brodmann (*BA*). The voxels show levels of significance above a threshold z=1.65, P=0.05, and a cluster size of k=20

	z	x	y	z	BA
Precuneus, left	2.80	–24	–68	36	7/19
Parietal inferior, left	3.63	–36	–72	28	39/40
Precuneus, right	2.51	20	–76	32	7/19
Parietal inferior, right	2.51	28	–64	28	39/40
Prefrontal, left	2.79	–4	8	56	6
Prefrontal, right	2.43	44	20	16	45

Discussion

The results of this study demonstrate activation patterns of distributed brain regions during episodic encoding and retrieval of paired word associates using a whole-brain EPI sequence and a single epoch paradigm.

For visualization of motor cortex or primary sensory activation, the repetitive delayed box-car design is the most frequently used paradigm (e.g., Bandettini et al. 1992). However, the design of our cognitive stimulation paradigm – one set of 12 word-pair associates – made it necessary to use a single-epoch delayed box-car paradigm, which means that one initial baseline was followed by the "activation" (encoding or retrieval) and was completed with a final baseline. We provide further evidence for the feasibility of this type of paradigm design in the study of higher cortical function supporting the work that has already been put forward by Buckner and colleagues (1996).

Since the introduction of fMRI (Belliveau et al. 1991) as a functional imaging tool, there have been several approaches to study human memory. However, most of the studies have employed methods resulting in partial brain coverage (Le Bihan et al. 1993; McCarthy et al. 1994; Demb et al. 1995; D'Esposito et al. 1995; Cohen et al. 1997; Gabrieli et al. 1997). Le Bihan and co-workers (1993) demonstrated activation of human visual cortex during visual recall with a single slice in an axial-oblique orientation along the calcarine fissure. McCarthy et al. (1994) used a single slice of 10 mm thickness through the frontal cortex in a spatial working-memory task. They found circumscribed activations in the right middle frontal cortex, the anterior cingulate, and the left middle frontal cortex. D'Esposito et al. (1995) presented a working-memory study, which indicated that the dorsolateral prefrontal cortex is involved in dual-task performance. They assumed that parts of the dorsolateral prefrontal cortex contribute to the so-called central executive memory, which controls attention and information flow to and from verbal and spatial short-term memory buffers. Their method was limited to four slices covering the frontal cortex. Demb and co-workers (1995), in a study of semantic encoding and retrieval using few (two and three, respectively) coronal slices to cover left inferior prefrontal cortex, showed that the quantity of activation in the left inferior prefrontal cortex function is independent of task difficulty. It was shown that, using eight slices parallel to the AC-PC line, prefrontal cortex along with parietal cortex appears to play a role in active maintenance of information in working memory (Cohen et al. 1997). In a study by Gabrieli et al. (1997), special emphasis was placed on the medial temporal lobe by using eight slices covering the hippocampus perpendicular to its axis. They found that different structures are responsible in familiar (anterior-medial temporal) and unfamiliar (posterio-medial temporal) information processing. Recently, Wagner and colleagues (1998) presented a study with whole-brain coverage on an incidental word-encod-

ing task and provided evidence that the amount of activation in a given brain region predicts the success in retrieving the encoded information.

We used whole-brain coverage with 26–32 slices (Shah et al. 1998) parallel to the AC-PC line, depending on the individual brain size. We chose the reference condition (nonsense-words) primarily to be able to subtract areas activated due to the visual input and further processing of letter strings which obey german spelling rules. However, there are still some limitations to be discussed according the remaining areas. The are at least three differences between the used reference condition and the experimental condition: words versus nonsense-words, greater cognitive effort in one task compared with the other, and retrieval of words compared with silent reading of nonsense-words. Thus, our results highlight brain areas with an increase in the BOLD-signal above a mental state where subjects perceive and read nonsense-words with a minor cognitive effort. We observed encoding-associated increases of the BOLD response bilaterally in the precuneus, bilaterally in the cerebellum, the anterior cingulate, the left and right frontal cortex, and in the left parahippocampal area. During retrieval, increases in the BOLD signal were seen bilaterally in the precuneus, in bilateral medial and inferior parietal cortex, the anterior cingulate, the right prefrontal cortex, the left dorsolateral prefrontal cortex, as well as in the dorsomedial thalamus on the left side.

Cognitive subtraction of encoding versus retrieval and vice versa showed several areas differentially more activated during encoding than during retrieval: bilateral cerebellar areas, a left frontopolar region spreading to the frontal medial cortex, as well as the left temporal lobe including the hippocampus and the inferior temporal lobe. Differentially more activation in bilateral precuneus, bilateral inferior and medial parietal cortex, and in the right inferior frontal cortex were found during retrieval versus encoding of word-pair associates.

Some of the recent studies have been carried out with whole-brain coverage (Spitzer et al. 1996; Stern et al. 1996; Busatto et al. 1997, Wagner et al. 1998) and just one study focused on distributed brain activation patterns in a memory task (Busatto et al. 1997). Using whole-brain coverage and a novel picture encoding task, Stern et al. (1996) provide evidence of activation-induced fMRI signal-intensity changes in human hippocampal formation. They analyzed the data, using a non-parametric approach, by placing the regions of interest in medial temporal lobe structures and fusiform gyrus. Spitzer et al. (1996) pointed out that an active control condition might be superior to a rest control condition in analyzing data from a semantic memory task. Busatto and coworkers (1997) presented a fMRI-study of episodic memory using whole-brain coverage with T2*-weighted images (14 slices). They found encoding and retrieval patterns associated with activation that were comparable to those found in previous PET studies. In contrast to previous PET experiments (Tulving and Markowitsch 1997), Busatto and co-workers did not observe activation in the left dorsolateral prefrontal cortex, but observed activation in Broca's area. They argue this might reflect the use of inner speech by subjects to aid encoding or retrieval.

Although it is known that the BOLD signal, as measured by fMRI methods, arises from microscopic magnetic susceptibility variations, which are themselves brought about by changes in blood oxygenation; macroscopic susceptibility effects arising from tissue boundaries, for example, also alter the MR signal in EPI-based techniques. This effect produces a significant artifact in prefrontal cortex because of the susceptibility differences between the ethmoidal air cells and brain tissue, resulting in partial or complete signal extinction from the frontal poles. Signal loss, its extent, and the associated geometric distortions, can be influenced by slice orientation and the chosen phase-encode direction. It is known that transverse slice orientation suffers especially from signal loss in the frontal areas (Ojemann et al. 1997). In this study, despite the aforementioned disadvantage, transverse slices were chosen to maximize presentation rate (which is also known to strongly influence activation levels) while maintaining near isotropic resolution.

We found, for encoding as well as for retrieval of word-pair associates, bilateral frontal lobe activations. With the cognitive subtraction method, we underline the HERA model in the interpretation of the role of the prefrontal cortex in episodic memory. The proposed left/right asymmetry (e.g., Tulving et al. 1994; Kapur et al. 1995) for episodic encoding and retrieval is dependent on the material specificity of the stored and retrieved material. There is a more right lateralization when objects have to be encoded (Moscovitch et al. 1995; Kelley et al. 1998) and a more left lateralization encoding words (Petersen et al. 1990; Kelley et al. 1998). Our verbal material consisted of high-imagery-content words containing some kind of object information coded in a letter string (i.e., word) and, therefore, the bilateral predominantly left prefrontal activation during encoding and retrieval might be explained. However, with direct cognitive subtraction, we could show that there is indeed a lateralization to the left for encoding and to the right during retrieval. In line with previous studies that reported an activation of the left dorsolateral prefrontal cortex during retrieval and focused attention (Schumacher et al. 1996; Warburton et al. 1996; Johannsen et al. 1997), we observed a similar pattern of activation of the left dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex connects mnemonic information with the preparation of action, a function which is of particular importance in working-memory processes (Fuster 1995). This function is needed during encoding as well as during retrieval, and that is probably the reason for the lack of activation found in the direct cognitive subtraction. A reason for the activation of bilateral supplementary motor areas during encoding and retrieval might be the use of inner speech to store the information (Busatto et al. 1997). The SMA is known to be involved in the motor planning of speech (Wise et al. 1991).

Furthermore, we have demonstrated the importance of the precuneus in episodic memory. Fletcher and coworkers (1995b) showed in PET studies with auditory stimulus presentation that "imageability" of paired associates affects activity (i.e., regional cerebral blood flow: rCBF) of the precuneus during retrieval. In our present design, we chose word-pair associates of high imagery content and presented them visually as in a previous PET study (Halsband et al. 1998). Encoding of such words is correlated with the use of mnemonic devices that involve a high degree of imaginability. This rather effective strategy in the storage and retrieval of associative memory tasks is called "imaginal memory" (Paulesu et al. 1993). The performance can be dramatically improved using visual imagery in connecting arbitrary events (Paivo et al. 1966). We have demonstrated that precuneus activation during retrieval is not only related to the imagery content of the encoded material, and we were able to demonstrate further that activation is independent of the stimulus modality (visual or auditory) (Krause et al. 1999a). There was further evidence for precuneus involvement during retrieval in a study in which we used structural equation modeling to demonstrate different cortical networks for encoding and retrieval. In this study, we showed the importance of precuneus in the network during encoding and retrieval of verbal material (Krause et al. 1999b). In the data presented here, we can furthermore indicate precuneus involvement during encoding in the functional topography.

We report a bilateral increase of cortical activity in the inferior and medial parietal cortex during retrieval in the present study. This is in agreement with PET studies that observed rCBF-changes in these regions (e.g., Fletcher et al. 1995a, 1995b) during episodic memory retrieval. This region was also activated during working memory processes (McCarthy et al. 1994; Schumacher et al. 1996; Cohen et al. 1997). Brain-activation studies during linguistic working memory tasks have determined a close relation between the inferior parietal cortex and Broca's area (Schumacher et al. 1996). The subjects did not vocalize during the task and, therefore, it would appear that the act of retrieving words, which are stored as associates in episodic memory-related areas, from semantic memory activates networks concerned with the production of speech (Wise et al. 1991). In line with this hypotheses is another, which suggests that language processing is closely related to working-memory networks and that the language regions in fact originated in evolution from a working memory network for linguistic utterances (Aboitiz and Garcia 1997).

In the present study, left medial temporal lobe structures were significantly activated during encoding of the word pairs. The coordinates of the center-of-mass activation are in line with recently published data on episodic memory processes (Gabrieli et al. 1997). There is neuropsychological evidence for the importance of temporal lobe structures in memory function (e.g., Penfield and Milner 1958; Corkin et al. 1970). In a recent study, we demonstrated the impact of left medial temporal lobe lesions on memory performance (Weckesser et al. 1998). With the loss of this brain region, the patients had a significant lower performance on a paired associate learning task than healthy subjects, despite the fact that there was a significant right hippocampal activation. Until recently, the whole medial-temporal region has been crucially implicated in declarative or explicit memory functioning. Recently, however, fMRI has been successfully applied in disentangling the functional role of separate areas in the temporal lobe system during encoding and retrieval of declarative information (Gabrieli et al. 1997).

Because the dorsomedial thalamus is a very small structure, we used a more lenient threshold in a hypotheses-based statistical evaluation. The significant increase in BOLD contrast during retrieval in left dorsomedial thalamic structures may demonstrate attentional gating, resulting in selection of specific neuronal networks (Goldman-Rakic and Porrino 1985) in the projection field of this area. Goldman-Rakic and Porrino (1985) found that frontal lobe areas as well as the anterior cingulate receive projections from dorsomedial thalamic structures in the rhesus monkey. Based on case reports, it was suggested that the thalamus provides the substrate for lexical-semantic function and may be part of a working memory network (Fuster 1995; Nadeau and Crosson 1997). The role of dorsomedial thalamic structures has also been shown in lesion studies in animals (e.g., Asanuma et al. 1985; Baleydier and Mauguiere 1987) or observed in neuropsychological deficits (e.g., Winocur et al. 1984; Hennerici et al. 1989; Hodges and McCarthy 1993; Clarke et al. 1994; Nadeau and Crosson 1997; Shuren et al. 1997) after isolated thalamic infarcts. On the other hand, the possibility also exists that activation of this additional area is due to visual processing of presented words (Petersen et al. 1990). However, previous PET studies indicate a role for thalamic structures, especially during retrieval (Fletcher et al. 1995b), but specific localization within the thalamus was not discussed. There has been the observation of antegrade and retrograde memory impairment in several patients (Hennerici et al. 1989). Previous lesion studies and horseradish experiments of the mediodorsal nucleus' projections in animals (Asanuma et al. 1985; Goldman-Rakic and Porrino 1985) and the syndrome in patients after isolated thalamic infarcts who showed impairment of retrieval of high-imagery-content words (Clarke et al. 1994; Nadeau and Crosson 1997; Shuren et al. 1997) are pointing towards the role of this structure. Having this in mind, we conclude that our results further indicate the role of the dorsomedial thalamus in episodic retrieval.

We found activation of anterior cingulate during encoding and retrieval of word-pair associates. This is in line with several functional imaging studies investigating different higher cortical functions (e.g., Fletcher et al. 1995a, 1995b; D'Esposito et al. 1995). This region has been proposed to be part of an anterior attentional system that is critical for response selection among competing, complex contingencies (Posner and Petersen 1990). There exist reciprocal connections to different

frontal, prefrontal, and parietal areas (Goldman-Rakic 1988). It seems that anterior cingulate is a rather unspecific brain area, which is activated during different kinds of long-term memory tasks (Fletcher et al. 1995a, 1995b). The lack of activation with direct cognitive subtraction is probably due to the fact that encoding and retrieval in our study required quite similar degrees of attention and/or concentration.

Our finding of cerebellar activation during encoding is in line with previously presented results obtained from lesion, functional imaging, or animal studies (Andreasen et al. 1995; Doyon et al. 1996; Schmahmann and Pandya 1997; Schmahmann and Sherman 1997), suggesting that the cerebellum also has remarkable capacities in higher cognitive function. Several cerebellar regions are especially involved during learning of motor skills (e.g., Doyon et al. 1996). In a PET study, Andreasen and coworkers (1995) found activation of different, predominantly left hemispheric, cerebellar regions during retrieval of short- or long-term memory contents. We postulate that the cerebellum may play a more general role during episodic memory processes.

Conclusion

We were able to show distributed patterns of activated brain regions, comprising prefrontal areas, anterior cingulate, parahippocampal areas, thalamus, parietal areas and cerebellar regions in episodic memory by use of a new whole-brain EPI sequence allowing acquisition of an arbitrary number of slices. With respect to the direct cognitive subtraction, our data are in line with the proposed left/right asymmetry for episodic-memory processes. However, our data provide an extension of this model because encoding and retrieval processes engage bilateral prefrontal cortical areas with an augmentation on the left side for encoding and on the right side for retrieval of word-pair associates. Our findings add further evidence for the involvement of the cerebellum in episodic memory. The circumscribed activation of the dorsomedial thalamus during retrieval of paired associates may point to a differential role for this structure. A very important finding is the activation of the precuneus not only during retrieval of word-pair associates, but also during encoding.

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